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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,305	06/05/2001	Victor J. Dzau	50025/003003	7095

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EXAMINER
MARVICH, MARIA

ART UNIT	PAPER NUMBER
1636	41

DATE MAILED: 06/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,305	DZAU ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 13-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 13-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 October 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 9 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: The specification contains tables on page 6-7 and on page 10-11 that are not suitable for publication as part of the specification. Tables must be deleted from specification and submitted as drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. This invention recites a method for preventing or treating an NFk-B-associated disease. The invention proposes as a method, the introduction of NFkB

decoys, dsDNA molecules that bind to NFkB transcription factors, to inhibit their function in patients. Potential disease targets of this invention include those at risk of developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis.

In its broadest sense, the invention reads on prevention or treatment of any of these diseases in humans through the introduction of double stranded NFkB decoy. Decoy gene therapy in 1993 was not a tested art and the unpredictability of using this invention was high due to the lack of methods or processes for its use in humans. Many parameters had not been addressed such as the dsDNA molecule to be used, the amount of DNA to be delivered, timing of administration, retention, and the stability of the NFkB decoy in the vessel walls.

The few in vitro assays with an NFkB binding element provided evidence in the prior art that decoy use *in vitro* has promise. However, *in vitro* and animal models have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of NFkB decoy molecules can be species and model dependent, it is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy. Multiple numbers of different pharmacological strategies to inhibit for example restenosis have proved futile (Popma **et al.** 1991, page 1426 col. 1 first paragraph, last sentence). "These disappointing results may be due in part to interspecies differences in the process of neointimal proliferation in humans and animal models or to the incomplete role of neointimal hyperplasia in the causation of human restenosis". To date the process of treating and preventing disease in humans still remains highly unpredictable by any method.

2) State of the art. Schwartz **et al.** teach (cited by applicant: page 61, first column, last paragraph) that "Solving the restenosis problem, the Achilles heel of interventional cardiology, is a major priority. Solutions must be suggested by approaching the problem in multiple animal models in a stepwise manner. Only when the mechanisms of action and proof of concept are clear should they be applied to further human trials." The state of the art at the time of invention had not provided for these factors. Experimental tools for NFkB decoy therapy in 1993 were quite limited and the state of the art of NFkB decoy therapy is not of high art to date.

Strategies to inhibit NFkB-associated diseases- developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis - in humans at the time of invention did not include decoy gene therapy. Proposed methods for gene transfer into humans at the time of invention and since comprise three major classes; 1) viral- adenovirus, retrovirus and Senjai 2) liposomal gene transfer using cationic liposomes 3) naked plasmid DNA transfer (Morishita **et al.**, 2001 page 106, first paragraph). As author further states in 2001 that " current in vivo methods for vascular gene transfer are still limited by the lack of efficiency and potential toxicity." Various techniques that are recited for local administration (quoted below and also found on page 10, line 11-19) fall in a category that was in 1994 called "the potential Achilles' heel of biotechnology" (Lincoff, et al. page 2070 last full paragraph). The limitations, obstacles, disadvantages of the available local delivery devices are described by Lincoff page 2075, first paragraph –2078 2nd paragraph) and include for example the following which appears to summarize the section "Despite the intuitive simplicity of delivering drugs through a catheter... a number of obstacles must be overcome before such treatment becomes clinical reality. These

may be summarized as follows: how to deliver, what to deliver, when to deliver, how to keep the drug in place long enough to achieve full activity, how to overcome the potential deleterious effects of inhibition of wound healing, how to identify patients most likely to benefit..." (page 2073 last paragraph). Therefore, the state of art of drug-delivery was not high at the time of invention.

3) Number of working examples. The specification provides no examples of claimed invention- the preparation of NFkB decoys in liposomes, delivery procedure or therapeutic assay.

4) Amount of guidance provided by applicants. The specification is silent with respect to what decoys and what methods would be utilized to perform this method in humans. The specification does not adequately teach how to effectively prevent or treat NFkB diseases or reach any therapeutic endpoint in humans. The Applicant does not provide *in vitro* binding inhibition assays or in vivo assays commensurate with the scope of the claims.

The specification provides as guidance for methods of treatment with the NFkB decoy only the following disclosure

> "The host is typically a mammal, usually a human. The selected method of administration depends principally upon the target cell, the nature of the decoy, the host, the size of the decoy. Exemplary methods are described in the examples below; additional methods including transfection with retrovirus, viral coat protein-liposome mediated transfection, lipofectin etc. are described in Dzau et al..." (page 9, line 17-23). "Various techniques can be provided for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access, or the like... Alternatively, systematic administration of the decoy using e.g. lipofection, liposomes with tissue targeting (e.g. antibody), etc. may be practiced. Systematic administration is most applicable where the distribution is limited to targeted cell types, e.g. virus-specific transcription factors limited to infected cells, mutant oncogenic transcription factors limited to transformed cells, etc.". (page 10, line 11-19)

The only provided specific disclosure is that the preferred mode of treatment with NFkB is introduction of such as a polymer or liposomes (table page 11).

This guidance provided by the applicants particularly does not provide for human patients with the potential or with the claimed diseases. There is no exemplary method provided. Additional methods listed are untested particularly as concerns the introduction of NFkB decoy or any other form of decoy molecules into humans. The various devices and techniques listed for local administration had yet to be adequately developed.

Safety and efficacy issues are at the forefront of research today in delivery techniques with a continued call for basic research on gene transfer vectors and gene delivery techniques. However, in 1993, methods for the transfer of NFkB decoy to a variety of organs required for this therapy such as heart, kidneys, skin, lymphatic, vasculature disease, or for ex vivo therapy for humans were not available either in the specification or the prior art. Since successful gene transfer depends upon the mode of gene transfer into the target cells and nuclei, no disclosure for a critical aspect of the invention, methods for treating or preventing said diseases in humans was not provided by applicant. Furthermore, other critical components of the invention have not been defined for human patients in this specification and for the art such as the amount of NFkB to prevent and treat disorders, timing of administration, retention and the stability of decoy in the vessel wall.

5) Nature of invention. The invention recites the production of NFkB decoys for the therapeutic treatment and prevention of developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection,

neoproliferative disorder or restenosis. This invention requires a combination of molecular cloning, viral and clinical techniques.

6) Level of skill in the art. The level of skill in the art covering this invention was not high at the time of invention. The development of HVJ liposomes for the preparation of NFkB decoys was rapidly advancing in the field. But the field of gene therapy was just beginning to emerge including preclinical trials and animal models.

7) Scope of the invention. This invention has broad scope in that it recites a method for the prevention and treatment of a wide variety of diseases i.e. ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis by introduction of a NFkB decoy.

Independent claim 13 and by dependency claims 14-27 recite "A method for the prevention or treating an NFkB-associated disease". In addition to the reasons stated above, these claims are not enabled for prevention of NFkB-associated diseases. In humans, the claimed diseases are usually established before therapy is offered. The specificity does not adequately teach how to effectively predict for whom the prevention would be required. In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in Applicant's for how to reasonably determine for what population the claimed invention is intended.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim reads on an NFkB dsDNA molecule that functions as a decoy to inhibit DNA binding of the NFkB transcription factor. Applicants do not provide a written description of said molecule.

The written description requirement for genus claims may be satisfied through sufficient description of a relevant a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics such as structure or other physical and/or chemical properties, by functional characteristics couple with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient

to show applicants were in possession of the claimed genus. In the instant case, applicants present working examples for *E2F decoy and PRE decoy* and provide general description of decoy molecules. Applicants provide no relevant identifying characteristics of other decoys with the same activity of claimed invention. It must be considered that decoy molecules with the ability to inhibit NFkB DNA binding must be empirically determined. It must be considered that the disclosed examples are not a representative number of species to show applicants were in possession of the claimed genus. It must be assumed that the skilled artisan would not conclude that applicant was in possession of claimed genus.

No claims are allowed.

Response to Amendment

The remarks filed under 37 CFR 1.10 filed 6/5/2001 are insufficient to overcome the rejection of claims 13-27 based upon 35 U.S.C. 112 first paragraph as set forth in this Office action because: the rejection is not solely based upon the prior art and the skilled artisan's ability to treat rats with NFkB-associated diseases.

Arguments by Susan M. Michaud for enablement of methods of use of NFkB decoys for the treatment of ischemic reperfusion injury, inflammatory arthritis, glomerulonephritis, cytokine production and tumor growth in rats are presented.

It is explained that operability of the NFkB decoys is shown in the enclosed papers that describe above results (page 7, last sentence)

> "The data described in each of the papers discussed above show that NFkB decoys are effective agents in the treatment of NFkB-associated diseases and conditions, as is specified in new claims 13-27"

But in the specification, we have no guidance as to what decoys and what methods would be utilized to perform this method in humans. Applicant presents no art recognized nexus between the results obtained in rats and the results the skilled artisan would expect to see in humans. Additionally, we have no guidance as to how to effectively predict for whom the prevention would be required. As stated above for claims rejections 13-27, the skilled artisan attempting to practice methods of treatment and prevention of NFkB –associated diseases with NFkB decoys would have needed to practice undue and excessive experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucell, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent analyst Kay Pinkney whose telephone number is (703) 305-3553.

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 3, 2002

DAVID GUZO
PRIMARY EXAMINER